Section I. (Amendments to the Claims)

Please amend claims 4-13 and 24-28, as set out below in the listing of claims 1- 28 of the application.

1. (currently amended) An isolated nucleotide sequence comprising a dystrophin minigene encoding a protein consisting of:

(a) a N-terminal domain;

(b) four to six rod repeats;

(c) an H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein; and

(d) a cysteine-rich domain,

wherein:
the N-terminal domain is selected from a group consisting of a N-terminal domain of the dystrophin protein, a modified N-terminal domain of the dystrophin protein, and a N-terminal domain of a utrophin protein;
the rod repeats are selected from a group consisting of rod repeats in the dystrophin protein, rod repeats in the utrophin protein, and rod repeats in a spectrin protein;
the cysteine-rich domain is the cysteine-rich domain of the dystrophin protein or the utrophin protein, and

wherein the dystrophin minigene is capable of ameliorating dystrophic pathology when expressed in a dystrophic muscle.

2. (currently amended) An isolated nucleotide sequence comprising a dystrophin minigene encoding a protein consisting of:

(a) a N-terminal domain;

(b) four to six rod repeats;

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(c) H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein;

(d) a cysteine-rich domain; and

(e) the last three amino acids of a C-terminal domain of the dystrophin protein, _____

wherein:_____
the N-terminal domain is selected from a group consisting of a N-terminal domain of the dystrophin protein, a modified N-terminal domain of the dystrophin protein, and a N-terminal domain of a utrophin protein; _____
the rod repeats are selected from a group consisting of rod repeats in the dystrophin protein, rod repeats in the utrophin protein, and rod repeats in a spectrin protein; _____
the cysteine-rich domain is the cysteine-rich domain of the dystrophin protein or the utrophin protein, and
_____
wherein the dystrophin minigene is capable of ameliorating dystrophic pathology when expressed in a dystrophic muscle.

3. (currently amended) An isolated nucleotide sequence comprising a dystrophin minigene encoding a protein or the complement of the dystrophin minigene, wherein the protein comprises:

(a) a N-terminal domain of a dystrophin protein or a modified N-terminal domain of the dystrophin protein;

(b) four to six rod repeats of the dystrophin protein;

(c) an H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein; and

(d) a cysteine-rich domain of the dystrophin protein, _____
_____

wherein said nucleotide sequence has fewer than 5,000 nucleotides.

4. (currently amended) The isolated nucleotide sequence of claim 3, wherein said protein further ~~comprising~~ comprises an H2 domain of the dystrophin protein, or an H3 domain of the dystrophin ~~gene~~

protein.

5. (currently amended) The isolated nucleotide sequence of claim 3, wherein said protein ~~containing~~ contains four rod repeats of the dystrophin protein.

6. (currently amended) ~~The isolated nucleotide sequence of claim 3, containing~~ An isolated nucleotide sequence comprising a dystrophin minigene encoding a protein or the complement of the dystrophin minigene, wherein the protein comprises:
(a) a N-terminal domain of a dystrophin protein or a modified N-terminal domain of the dystrophin protein;
(b) five rod repeats of the dystrophin protein;

(c) an H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein; and

(d) a cysteine-rich domain of the dystrophin protein, wherein said nucleotide sequence has fewer than 5,000 nucleotides.

7. (currently amended) ~~The isolated nucleotide sequence of claim 3, containing~~ An isolated nucleotide sequence comprising a dystrophin minigene encoding a protein or the complement of the dystrophin minigene, wherein the protein comprises:
(a) a N-terminal domain of a dystrophin protein or a modified N-terminal domain of the dystrophin protein;
(b) six rod repeats of the dystrophin protein;

(c) an H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein; and

(d) a cysteine-rich domain of the dystrophin protein, wherein said nucleotide sequence has fewer than 5,000 nucleotides.

8. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:2, or which is the complement of SEQ ID NO:2.

9. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:6, or which is the complement of SEQ ID NO:6.

10. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:9, or which is the complement of SEQ ID NO: 9.

11. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:10, or which is the complement of SEQ ID NO:10.

12. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:12, or which is the complement of SEQ ID NO:12.

13. (currently amended) The isolated nucleotide sequence ~~of claim 3,~~ consisting of SEQ ID NO:14, or which is the complement of SEQ ID NO:14.

14. (original) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 1 operably linked to an expression control element.

15. (original) The recombinant adeno-associated virus vector of claim 14, wherein the expression control element is an MCK promoter or a CMV promoter.

16. (currently amended) A recombinant adeno-associated virus vector, comprising any one of the nucleotide ~~sequence~~ sequences of ~~claim~~ claims 8, 9, 10, 11, 12 and 13, operably linked to an expression control element.

17. (original) The recombinant adeno-associated virus vector of claim 16, wherein the control element is an MCK promoter or a CMV promoter.

18. (cancelled)

19. (cancelled)

20. (cancelled)

21. (cancelled)

22. (cancelled)

23. (cancelled)

24. (previously presented) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 9, operably linked to an expression control element.

25. (previously presented) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 10, operably linked to an expression control element.

26. (previously presented) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 11, operably linked to an expression control element.

27. (previously presented) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 12, operably linked to an expression control element.

28. (previously presented) A recombinant adeno-associated virus vector, comprising the nucleotide sequence of claim 13, operably linked to an expression control element.

Section III. REMARKS

Submission of Revocation of Prior Power of Attorney and Appointment of New Attorneys of Record

Enclosed and submitted herewith (in Appendix A hereof) is a Revocation of Prior Power of Attorney and Appointment of New Attorneys of Record, in which the applicant revokes the power of all prior attorneys/agents of record, and appoints the undersigned attorney and attorneys of his firm as attorneys of record in this application.

Amendment of the Specification

The title of the application at page 1 thereof has been amended herein for consistency with the claims, and to correct same (see Examiner Whiteman's remark at page 3, lines 16-17 of the June 30, 2003 Office Action, "an isolated nucleotide sequence does not 'encode' a minigene although they [sic] may comprise a minigene").

The title of the application is now appropriately set forth as "DNA sequences comprising dystrophin minigenes and methods of use thereof."

Amendment of Claims to Overcome Objections and Place Same in Form for Issue

In the May 25, 2004 Office Action, the examiner stated that "Claims 6-13, 16, 17, and 24-28 are free of the prior art of record" (page 4, line 11), but held such claims to be objectionable "as being dependent upon a rejected base claim" and as being "allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims" (page 4, lines 12-14 of the May 25, 2004 Office Action).

In response, claims 6-13 have been rewritten so that each is now in independent form. Accordingly, claims 6-13 are now in form for allowance and issue.

Consistent therewith, claim 16, which is multiply dependent under claims 8, 9, 10, 11, 12 and 13, is likewise in form for allowance and issue, since each of the depended-from claims 8, 9, 10, 11, 12 and 13 has been rewritten in independent form.

Claim 17 depends from claim 16, and is correspondingly allowable.

Since claims 24-28 recite the nucleotide sequences of claims 9-13, respectively, the rewriting of claims 9-13 in independent form obviates the objection to claims 24-28, and such claims also are in form and condition for allowance.

In addition to the foregoing amendments to place claims in independent form, claims 1-5 and 16 have been amended herein to place same in better form.

Claims 1-3 have been amended to insert spacings into the text of the claims, to more clearly demarcate the text in subparagraph format appropriate to specific limitations in the claims. As such, claims 1-3 are now in better form for consideration by the examiner and subsequent allowance.

Claim 4 has been amended to recite:

> **4. The isolated nucleotide sequence of claim 3, wherein said protein further ~~comprising~~ comprises an H2 domain of the dystrophin protein, or an H3 domain of the dystrophin ~~gene~~ protein.**

Such amendment thereby improves the wording of the claim, in relating the nucleotide sequence to its expression product.

Claim 5 has been amended in an analogous manner:

> **5. The isolated nucleotide sequence of claim 3, wherein said protein ~~containing~~ contains four rod repeats of the dystrophin protein.**

Claim 16 has been amended herein to recite the recombinant adeno-associated virus vector as comprising "any one of the nucleotide ~~sequence~~ sequences of ~~claim~~ claims 8, 9, 10, 11, 12 and 13," to improve the grammatical character of such claim.

Based on all of the foregoing, claims 6-13, 16, 17 and 24-28, indicated free of the art and prospectively allowable in the May 25, 2004 Office Action, are now in form and condition for allowance.

Rejection of Claims on §102(e) Grounds, and Traversal Thereof

In the May 25, 2004 Office Action, claims 1-5 and 14-15 were rejected under 35 U.S.C. §102(e) as being anticipated by Chamberlain et al. U.S. Patent Publication No. 20003/0216332 (hereafter "Chamberlain").

This rejection is traversed on the basis of the Declaration of the applicant enclosed and submitted herewith (in Appendix B hereof) under the provisions of 37 CFR §1.131.

The applicant's §1.131 Declaration attests to facts relating to the applicant's conception and making of the invention of claims 1-5 and 14-15 prior to the effective date of Chamberlain, and evidence of the applicant's activities and efforts in advancement of the Invention subsequent to its original conception.

The facts and evidence adduced in the §1.131 Declaration remove Chamberlain as 35 USC §102(e) prior art against claims 1-5 and 14-15, and therefore overcome the rejection of such claims in the May 25, 2004 Office Action based on such reference.

In the §1.131 Declaration, the applicant, Xiao Xiao, attests to his invention of the subject matter claimed in the claims of the present application, as directed to an isolated nucleotide sequence comprising a dystrophin minigene encoding a protein having the following features: (a) a N-terminal domain; (b) four to six rod repeats; (c) an H1 domain of a dystrophin protein and an H4 domain of the dystrophin protein; and (d) a cysteine-rich domain ("Invention").

The applicant declarant in the §1.131 Declaration acknowledges his awareness of the §102(e) rejection of claims to the Invention in the May 25, 2004 Office Action, and declares that the present application claims the priority of U.S. Provisional Patent Application No. 60/200,777 filed in the declarant's name on April 28, 2000 for "DNA SEQUENCES ENCODING DYSTROPHIN MINIGENES AND USE THEREOF" ("Xiao Provisional Application") and that declarant is the sole inventor of the subject matter disclosed in the Xiao Provisional Application.

The applicant declares in the §1.131 Declaration that the Invention was made prior to the October 6, 2000 effective date of Chamberlain, as evidenced by the subject matter that the applicant has described in the Xiao Provisional Application, including the following disclosures thereof (identified by page and line number(s) in the specification of such provisional patent application):

(a) page 4, lines 17-21 ("[a]lthough the [prior art] mini-genes contained ... 1 to 3 central rod repeats, they were ... insufficient to protect muscle from dystrophic pathology") excluding 1 to 3 rod constructs from the scope of the invention;

(b) page 6, lines 2-4 ("[t]he present invention provides the dystrophin gene which can be successfully reduced to approximately one third (1/3) of its 11 kb full-length coding sequence, without compromising essential functions in protecting muscles from dystrophic phenotypes");

(c) page 7, lines 3-6 ("Dystrophin has four major domains: the N-terminal domain (N), the cysteine-rich domain (CR), the C-terminal domain (CT) and the central rod domain, which contains 24 rod repeats (R) and 4 hinges (H). The mini-dystrophin genes were constructed by deleting a large portion of the central rods and nearly the entire CT domain (except the last 5 amino acids");

(d) page 53, lines 4-6 ("novel truncated dystrophin genes, which are small enough to be packaged into AAV vectors, and yet retain the essential functions needed to protect muscle from the pathological symptoms");

(e) page 55, lines 8-10 ("novel dystrophin constructs created by extensive deletions in the central rod domain, plus extensive deletions in the C-terminal domain of the human dystrophin cDNA");

(f) page 55, lines 12-13 ("[t]he mini-dystrophin genes are smaller than the 5-kilobase packaging limit of AAV viral vectors");

(g) page 56, lines 8-9 ("a major portion of the rod domain is dispensable") and lines 14-15 ("[w]e have created by rational design several mini-genes, in each deleting up to ¾ of the central rod domain"), which within the limits of accuracy of "rational design" can involve deletion of up to 20 of the 24 naturally-occurring rod repeats (in which ¾, when expressed as a decimal fraction of relevant significant digits (= 0.8), yields a rod domain deletion portion = 0.8 x 24 rods = 19.2 rods, which in turn due to the whole number character of repeat units requires deletion of 20 of the 24 naturally-occurring rods, to produce a 4-rod construct);

(h) page 60, lines 5-7 ("[t]o accommodate as many rod units in the central domain without exceeding the AAV vector packaging limit, we have for the first time deleted the entire C-terminus (819 bp) without sacrificing the primary functions of dystrophin") and lines 19-22 ("Mini-genes Δ3849" and "Mini-gene Δ3990" as 5-rod constructs, and "Mini-gene 4173" as a 6-rod construct);

(i) page 62, lines 7-8 ("[t]he entire gene expression cassettes can be readily packaged into adeno-associated virus (AAV) vectors"); and

(j) page 62, lines 12-14 ("the present invention further defines the minimal functional domains of dystrophin and provides ways to optimize and create new versions of mini-dystrophin genes").

The applicant notes in the Declaration that disclosure cited by the Examiner in the May 25, 2004 Office Action, at page 56 of the Xiao Provisional Application ("[t]o ensure sufficient physical flexibility of the protein, all of our mini-dystrophins still retain at least 5 rod repeats...in the central rod domain") describes specific illustrative constructs selected for protein physical flexibility, within the scope of broader disclosure of the Invention evidenced by the textual portions of the Xiao Provisional Application quoted in sub-paragraphs (a)-(j) of Paragraph 5 of the Declaration.

In like manner, the applicant notes in the Declaration that disclosure cited by the Examiner in the May 25, 2004 Office Action, at page 60 of the Xiao Provisional Application ("the mini-dystrophin genes reported here accommodated at least 5 rod repeats") also describes specific illustrative constructs within the scope of broader disclosure of the Invention in the Xiao Provisional Application, with reference to the same textual portions of such provisional patent application.

The applicant in the Declaration attests to the fact that the April 28, 2000 filing date of the Xiao Provisional Application is prior to the October 6, 2000 effective date of Chamberlain.

The applicant in the Declaration also attests to the fact that the broad disclosure of the Invention in the Xiao Provisional Application evidences the constructive reduction to practice of the Invention as of the April 28, 2000 filing date of the Xiao Provisional Application, involving a mini-dystrophin gene encoding a protein having a N-terminal domain, a cysteine-rich domain, hinge domains H1 and H4, and a number of rod repeats defined by deletion of a "large portion" (page 7, lines 3-6)/"major portion" (page 56, lines 8-9) of the 24 naturally-occurring rod repeats, producing a truncated form of the dystrophin gene with "extensive deletions in the central rod domain" (page 55, lines 8-10) that:

(A) excludes 1 to 3 rod constructs (page 5, lines 17-21);

(B) includes deletion of "up to ¾ of the central rod domain" (page 56, lines 14-15), which within the limits of accuracy of "rational design" (page 56, line 15) can involve deletion of up to 20 of the 24 naturally-occurring rod repeats, yielding a 4-rod construct;

(C) includes 5-rod and 6-rod constructs (page 60, lines 19-22), and

(D) is sufficiently small for packaging in an AAV vector without loss of function (page 53, lines 4-6).

The Declaration also attaches in **Exhibit 1** thereof additional evidence of conception of the Invention prior to the effective date of Chamberlain, in the form of pages (pages 1 (Face Page), 2, 81-82, 104 and

105) of a grant application submitted to the U.S. Department of Health and Human Services, in which relevant dates are blacked out, but which dates are prior to the effective date of Chamberlain. The enclosed pages of this grant application contain the following disclosure:

(i) an identification of a proposed grant project entitled "Improving Muscle Function Through Gene Delivery" (page 1 (Face Page));

(ii) an identification of the applicant ("Dr. Xiao") as responsible for Project 1, entitled "Adenoassociated virus (AAV) vectors to improve mature muscle function by gene delivery" (page 2);

(iii) disclosure of a dystrophin mini-gene lacking the central rod domain, with only one central rod (page 81-82);

(iv) hypothesis of a single-rod dystrophin mini-gene as improving the function of dystrophin-deficient muscle when delivered by AAV vectors (page 104) and

(v) description of alternative work in the event that the single rod construct were not to produce significant functional recovery, including removal of a portion of the C-terminal region to "empty some space for additional rod domains to be incorporated" (page 105), whereby numbers of rods greater than one would be evaluated in constructs compatible with AAV vectors.

Further, the applicant attests in the Declaration that following his original conception of the Invention, he undertook various activities and efforts to advance the Invention, including:

(i) his submission in February, 2000 to the American Society of Gene Therapy (ASGT) of an Abstract ("Efficient Functional Correction of Muscular Dystrophy in mdx Mice by AAV Vectors Carrying Novel Human Mini-dystrophin Genes") describing "for the first time the successful gene therapy of DMD using AAV vectors" using "a series of novel mini-dystrophin genes (3.8 kb to 4.2 kb) that readily package into AAV along with an MCK (muscle-specific creatine kinase) promoter to assure tissue-specific transgene expression"), which was published on-line by the ASGT on May 1, 2000 in Molecular Therapy, Vol. 1, No. 5, May 2000, Part 2, a true and exact copy of which is attached in **Exhibit 2** of the Declaration,

(ii) the applicant's corresponding oral presentation on the Invention and appertaining research results at the ASGT Third Annual Meeting, at 2:00 PM on June 1, 2000,

(iii) the applicant's submission in July, 2000 to the Proceedings of the National Academy of Sciences of the United States of America of a manuscript entitled "Adeno-associated virus vector carrying human minidystrophin genes effectively ameliorates muscular dystrophy in *mdx* mouse model," which was published in such Proceedings in its December 5, 2000 issue, Vol. 97, No. 25, pages 13714-13719, a true and exact copy of which is attached in **Exhibit 3** of the Declaration; and

(iv) the applicant's filing on April 30, 2001 of the present application.

The applicant's Declaration therefore is submitted to present evidence of the applicant's conception and making of the Invention prior to the effective date of Chamberlain, and evidence of the applicant's activities and efforts in advancement of the Invention, in order to remove Chamberlain as prior art under 35 USC §102(e) against claims 1-5 and 14-15 rejected on the basis of such reference.

In view of the facts and documentary evidence attested to in the applicant's §1.131 Declaration, antedating Chamberlain and removing it as 35 USC §102(e) prior art, applicant respectfully requests withdrawal of the §102(e) rejection of claims 1-5 and 14-15.

Fees Payable for Rewritten Independent Claims 6-13

The rewriting of claims 6-13 in independent form herein has increased the number of independent claims by eight (8), in relation to the number of independent claims for which payment previously has been submitted in this application. No net addition of total claims has been effected.

An added claims fee of 8 × $43.00 = $344.00 is due.

Payment of such added claims fee of $344.00 is enclosed in the form of a Credit Card Authorization Form in such amount.

Any additional fee or charge properly payable in connection with the filing and entry of this Amendment hereby is authorized to be charged to Deposit Account Number 08-3284 of Intellectual Property/ Technology Law.

CONCLUSION

Claims 6-13, 16, 17 and 24-28, indicated free of the art and prospectively allowable in the May 25, 2004 Office Action, are now in form and condition for allowance. The §102(e) rejection of claims 1-5 and 14-15 based on Chamberlain has now been overcome by the §1.131 Declaration of the applicant enclosed in Appendix B hereof.

Accordingly, all pending claims 1-17 and 24-28 are now in form and condition for allowance. The examiner is therefore respectfully requested to reconsider such pending claims in light of the foregoing amendments and remarks herein, and to correspondingly issue a Notice of Allowance for the application.

If any issues remain outstanding, incident to the formal allowance of the application, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss such issues to facilitate their resolution, so that the present application can be passed to issue at an early date.

Respectfully submitted,

Steven L. Hultquist
Reg. No. 28,021
Attorney for Applicant

**INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
P.O. Box 14329
Research Triangle Park, NC 27709
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File No.: 4247-101**